Baxter Healthcare Ltd.
Caxton Way, Thetford
Norfolk IP24 3SE
Great Britain

Baxter

PL.0116/0201
RA.840
HEMOFIL M, ANTIHAEMOPHILIC FACTOR (HUMAN)
METHOD M, MONOCLONAL PURIFIED

PART III: I: MLA.201, DATA SHEET, EXPERT REPORTS
III: TOXICOLOGICAL AND PHARMACOLOGICAL DOCUMENTATION
V: PACKAGING AND LABELLING

T04

VOL.3 OF 3

V. PACKAGING AND LABELLING

1. Introduction

Antihaemophilic Factor (Human), Method M, HEMOFIL® M is to marketed as a lyophilised product in a USP Type 1 glass container with a blue chlorobutyl rubber closure, and protective aluminium cap.

The product will be sold according to the approximate international units of AHF activity contained in each bottle: three codes are envisaged:

Approximately 250 I.U./bottle
Approximately 500 I.U./bottle
Approximately 1000 I.U./bottle

Each of these codes will be supplied in a unit carton; a separate carton will contain the following ancillary products:

a) A Ph.Eur. Type 1 glass container holding 10 ml of Water for Injections Ph.Eur. (diluent).
b) A sterile, double-ended reconstitution device.
c) A sterile 15µ filter spike.
d) A 10 ml plastic syringe.
e) A 23 Ga. miniset, administration set.
f) "Directions for Use" package insert.

Devices b), c), d) and e) will be manufactured by Companies and Facilities registered under the Department of Health Manufacturers Registration Scheme (Sterile Products category).

2. Label copy

2.1 Proposed text for HEMOFIL® M bottle

BAXTER/HYLAND Wordmarks — 10 ml size, dried

HEMOFIL® M — 250/500/1000 I.U.

ANTIHAEMOPHILIC FACTOR (HUMAN)
Method M, Monoclonal Purified

For Intravenous Administration

Reconstitute at room temperature with 10 ml Water for Injections Ph.Eur. Administer within one hour of reconstitution. Do not refrigerate after reconstitution. Do not use if a gel forms on reconstitution.

When reconstituted contains approximately 12.5 mg/ml Albumin (Human), 0.15 mg/ml polyethylene glycol 3350, 0.055 M histidine and 0.030 M glycine as stabilising agents.

STORE BETWEEN 2 AND 8°C

Protect from light.

WARNING: The risk of transmitting hepatitis or other viral diseases may be present. Read direction insert and use as directed by physician.

This bottle contains X I.U. of AHF activity.

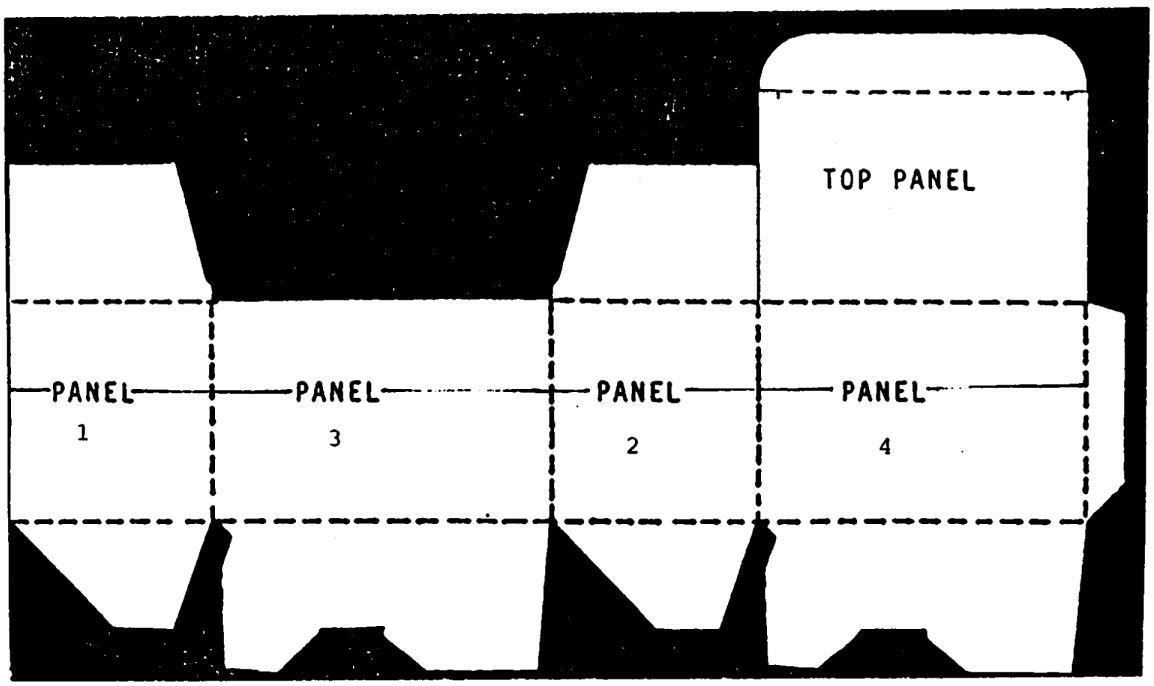
Lot No.: Expiry Date:

Manufactured by: Hyland Division of Baxter Healthcare Corporation, Glendale, CA 91202.

Distributed by: Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk. PL.0116/XXXX
PA.167/X/X POM

2.2 Proposed Text for Unit Carton

2.2.1 HEMOFIL^{R} M



A. TOP PANEL: 10 ml size, dried ANTIHAEMOPHILIC FACTOR (HUMAN), METHOD M, MONOCLONAL PURIFIED HEMOFIL® M — List No. FD060-XXX — 250/500/1000 I.U.

B. TOP SECTION SIDE PANELS

- FD060-XXX — 10 ml size, dried
BAXTER/HYLAND LOGO

HEMOFIL® M — 250/500/1000 I.U.

ANTIHAEMOPHILIC FACTOR (HUMAN), METHOD M, MONOCLONAL PURIFIED

C. BOTTOM SECTION, SIDE PANELS -

PANEL 1: STORE THIS PACKAGE BETWEEN 2-8°C.

Protect from light.

Administer within one hour after reconstitution.

This lot contains XXX International Units of AHF Activity per vial.

Lot No.:

Expiry Date:

PANEL 2: Blank

PANEL 3: Content: One bottle of 10 ml Antihaemophilic Factor (Human).

FOR INTRAVENOUS ADMINISTRATION: See enclosed direction sheet and use as directed by physician.

When reconstituted to the appropriate volume this product contains approximately 12.5 mg/ml Albumin (Human), 0.15 mg/ml polyethylene glycol 3350, 0.55 M histidine and 0.030 M glycine as stabilising agents.

WARNING: The risk of transmitting hepatitis or other viral diseases may be present. Read direction insert and use as directed by physician.

Manufactured by: Hyland Division of Baxter Healthcare Corporation, Glendale, CA91202 and Lessines, Belgium.

Distributed by: Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk.

PL.0116/XXX
PA.167/X/X POM

Note: Should there be insufficient room on Panel 3 for all of this information, certain portions may be moved onto Panel 1.

PANEL 4: Blank

2.2.2 Accessories

The carton containing the assessory products will contain the following information:

BAXTER/HYLAND Logo

Accessory carton for HEMOFIL^{R} M

Antihaemophilic Factor (Human), Method M, Monoclonal Purified

Contents: One bottle of 10 ml Water for Injection Ph.Eur. (PL.0116/XXXX); one double-ended reconstitution device; one filter needle, one 10 ml syringe and one 23 Ga. miniset.

Store below 25°C. Avoid freezing to prevent damage to the diluent bottle.

Manufactured by
Hyland Division
N.V. Baxter S.A.
7860 Lessines (Belgium)

Distributed by
Baxter Healthcare Ltd.,
Thetford, Norfolk.

2.3 Proposed Text for Data Sheet

Data Sheet	BAXTER/HYLAND Wordmarks
HEMOFIL® M	Antihaemophilic Factor (Human), Method M, Monoclonal Purified

Presentation

Antihaemophilic Factor (Human) Method M, HEMOFIL® M, is a sterile, stable, nonpyrogenic, dried preparation of antihaemophilic factor (Factor VIII, Factor VIII:C, AHF) in concentrated form with a specific activity range of 2 to 15 AHF International Units/mg of total protein. When reconstituted with the appropriate volume of diluent, it contains approximately 12.5 mg/ml Albumin (Human), 1.5 mg/ml polyethylene glycol (3350), 0.055 M histidine and 0.030 M glycine as stabilising agents. In the absence of the added Albumin (Human), the specific activity is approximately 2,000 AHF International Units/mg of protein. It also contains trace amounts of mouse protein at less then 10 ng/100 AHF activity units. See Clinical Pharmacology.

HEMOFIL® M is prepared by the Method M process from pooled human plasma by immunoaffinity chromatography utilising a murine monoclonal antibody to Factor VIII:C, followed by an ion exchange chromatography step for further purification. Method M also includes an organic solvent (tri(n-butyl) phosphate) and detergent (Triton X-100) virus inactivation step designed to reduce the risk of transmission of hepatitis and other viral diseases.

HEMOFIL® M is a high purity AHF concentrate which contains only trace amount of fibrinogen or other proteins. Each carton and bottle of Antihaemophilic Factor (Human), HEMOFIL® M is labelled with its AHF content, expressed in International Units (WHO) of AHF activity per bottle.

Uses

The use of Antihaemophilic Factor (Human), HEMOFIL® M, is indicated in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes.

HEMOFIL® M can be of significant therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per ml. However, in such uses, the dosage should be controlled by frequent laboratory determinations of circulating Factor VIII levels.

Antihaemophilic Factor (Human) is not indicated in von Willebrand's disease.

Dosage and Administration

Each bottle of Antihaemophilic Factor (Human), HEMOFIL[R] M, is labelled with the AHF content expressed in International Units per bottle. This potency assignment is referenced to the World Health Organisation International Standard.

The following formulae can be used to calculate the appropriate dose required for a given response (a) or the response to be expected from a given dose (b). These dosage formulae are presented for reference and as guidelines. The amount of AHF that an individual haemophiliac requires for normal haemostasis varies with circumstances and with the patient. Exact dosage determinations should be based on the medical judgment of the physician regarding circumstances, condition of the patient, degree of Factor VIII deficiency and the level of AHF to be achieved.

a) Units required =

body weight (kg) x 0.4 units/kg X
desired AHF increase (% of normal)

Example: 70 kg x 0.4 units/kg x 50% = 1,400 units

b) Expected AHF increase (% of normal) =

$$\frac{\text{units administered}}{\text{body weight (kg) x 0.4 units/kg}}$$

Example: $\frac{1{,}400 \text{ units}}{70 \text{ kg x } 0.4 \text{ units/kg}} = 50\%$

The response factor used in the preceding formulae (0.4 units/kg) was based on the work of Shanbrom and Thelin with adults: they reported that 3.8 to 4.0 units per kg bodyweight produce an increase of 10% (of normal) in AHF level. Abildgaard, et al, in work with boys 8 months to 14 years of age reported data from which a response factor of 0.5 units/kg can be calculated: they reported that 1.0 unit per kg body dose weight produces an AHF increase of 2% (of normal).

Kasper has found that minor haemorrhagic episodes will generally subside with a single infusion if an AHF level of 30% (of normal) or more is attained. For more serious haemorrhages, and AHF level of 35 to 50% of normal should be obtained for optimum clot formation. In surgery, Kasper recommends that the first dose of Factor VIII, to achieve a level of 80 to 100% of normal, should be given an hour before the procedure. A second dose of Factor VIII half the size of the priming dose should be given about 5 hours after the priming dose. If several units of blood were lost during the operation, a third dose of concentrate should be given when the patient reaches the recovery room. The Factor VIII level should be maintained at a daily minimum of at least 30% for a healing period of 10 to 14 days.

Antihaemophilic Factor (Human) is to be administered only by the intravenous route. This material should be reconstituted, using aseptic technique, with the appropriate volume of Water for Injections Ph.Eur. Use within one hour of reconstitution.

Preparations of Antihaemophilic Factor (Human) HEMOFIL^{R} M, can be administered at a rate of up to 10 ml per minute with no significant reactions.

As a precautionary measure, the physician should determine the pulse rate before and during administration of the AHF concentrate. Should a significant increase of pulse rate occur, reduce the rate of administration or discontinue.

Contraindications

None known.

Warning

This product is prepared from pooled units of human plasma which have been individually tested and found nonreactive for hepatitis B surface antigen and negative for antibody to human immunodeficiency virus (HIV) by F.D.A. approved tests, and have been shown to have alanine aminotransferase (ALT) levels not exceeding two times the upper limit of normal. Other screening procedures are used to reduce the risk of transmitting viral infection. However, testing methods are not sensitive enough to detect all units of potentially infectious plasma and treatment methods have not been shown to be totally effective in eliminating viral infectivity from this product. Transmission of infection cannot, therefore, entirely be excluded.

As Antihaemophilic Factor (Human), HEMOFIL^{R} M, contains trace amounts of mouse protein, the possibility exists that patients treated with this product may develop hypersensitivity to the mouse proteins.

Precautions

General

Identification of the clotting deficiency as one of Factor VIII is essential before the administration of Antihaemophilic Factor (Human) is initiated. No benefit will be derived from this product in treating other deficiencies.

The Method M process significantly reduces the presence of blood group specific antibodies in the final product. Nevertheless, when large or frequently repeated doses are needed, as when inhibitors are present or when pre- and post-surgical care is involved, patients of blood groups A, B, and AB should be monitored for signs of intravascular haemolysis and decreasing haematocrit values. Haemolytic anaemia, when present, may be corrected by the administration of compatible Group O Red Blood Cells (Human).

Disposable plastic syringes should be used with this product.

Pregnancy

Animal reproduction studies have not been conducted with Antihaemophilic Factor (Human). It is also not known whether Antihaemophilic Factor (Human) can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Antihaemophilic Factor (Human) should be given to a pregnant woman only if clearly needed.

Laboratory Tests

Although dosage can be estimated by the calculations above, it is strongly recommended that, whenever possible, appropriate laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate AHF levels have been reached and are maintained.

If AHF fails to reach expected levels or if bleeding is not controlled after apparently adequate dosage, the presence of inhibitor should be suspected. By appropriate laboratory procedures, the presence of inhibitor can be demonstrated and quantified in terms of AHF units neutralised by each ml of plasma or by the total estimated plasma volume. If the inhibitor level is low (i.e. <10 Bethesda Units per ml), after sufficient dosage to neutralise inhibitor, additional dosage produces predicted clinical response. It should be noted that when inhibitor is present, measurement of Lee-White clotting time may be a better index of adequacy of dosage than measurement of circulating AHF.

Adverse Reactions

Allergic reactions may be encountered from the use of AHF concentrate preparations. Symptoms may include hives, urticaria, wheezing, tightness of the chest, or hypotension. and anaphylaxis. An unusual taste is occasionally noted after AHF infusions.

The protein in greatest concentration in Antihaemophilic Factor (Human), Method M, is Albumin (Human). Reactions associated with albumin are extremely rare, although nausea, fever, chills or urticaria have been reported.

Pharmaceutical Precautions

Antihaemophilic Factor (Human), HEMOFIL^{R} M, should be stored under refrigeration (2 to 8°C). Freezing should be avoided as breakage of the diluent bottle may occur.

Legal Category

Prescription Only Medicine.

Package Quantities

Antihaemophilic Factor (Human), HEMOFIL^{R} M, is available as single dose bottles. Each bottle is labelled with the potency in International Units, and is provided with 10 ml of Water for Injection Ph.Eur., a double-ended reconstitution device, a filter spike, a 10 ml syringe and a 23 Ga. miniset.

Unit Size	Approximate Activity	Code Number
10 ml	250 I.U./Bottle	FD-060-XXX
10 ml	500 I.U./Bottle	FD-060-XXX
10 ml	1000 I.U./Bottle	FD-060-XXX

Further Information

Nil

Product Licence Number PL.0116/XXXX
Product Authorisation Numbers PA.167/X/X

Date of Preparation

BAXTER wordmark

BAXTER Healthcare Ltd.,
Thetford, Norfolk, England.

Telephone: Thetford (0842) 754581

2.4 Proposed Text For "Directions for Use" Package Insert

The text for "Directions for Use" insert will constitute the following:

Data Sheet (2.3) Sections:	Additional Sections (see below)
PRESENTATION	CLINICAL PHARMACOLOGY
USES	Reconstitution:
DOSAGE AND ADMINISTRATION	Administration:
CONTRAINDICATIONS	Rate of Administration:
WARNINGS	
PRECAUTIONS	
General,	
Pregnancy	
Laboratory Tests	Information for patients
ADVERSE REACTIONS	
PHARMACEUTICAL PRECAUTIONS	HOW SUPPLIED REFERENCES

ADDITIONAL SECTIONS

CLINICAL PHARMACOLOGY

Antihaemophilic Factor (AHF) is a protein found in normal plasma which is necessary for clot formation.

The administration of Antihaemophilic Factor (Human), HEMOFIL® M, provides an increase in plasma levels of AHF and can temporarily correct the coagulation defect of patients with haemophilia A (classical haemophilia). The administration of Antihaemophilic Factor (Human) will also correct deficiencies caused by circulating inhibitors when the inhibitor level does not exceed 10 Bethesda Units per ml.

The half-life of Antihaemophilic Factor (Human), HEMOFIL® M, administered to Factor VIII deficient patients has been shown to be 14.8 ± 3.0 hours.

Use of an organic detergent/solvent (tri(n-butyl) phosphate/ Triton X-100) in the manufacture of Antihaemophilic Factor (Human) has little or no effect on AHF activity, while lipid enveloped viruses, such as hepatitis B and human immunodeficiency virus (HIV) are inactivated (1). Prince, et al, report inactivation of at least 10,000 Chimpanzee Infectious Doses (CID-50) of hepatitis B virus, 10,000 CID-50 of hepatitis non A, non B virus, and 30,000 Tissue Culture Infectious Doses of HIV with TNBP/detergent treatment during manufacture of an Antihaemophilic Factor (Human) concentrate (2).

The effectiveness of the Method M organic solvent/detergent inactivation step in reducing viral infectivity was assessed in vitro by using marker viruses. When known quantities of Sindbis virus, Vesicular Stomatitis virus, and Pseudorabies virus were added during manufacture, this step was shown to inactivate 3 to 4 logs of these viruses. The infectivity of HIV seeded into cryoprecipitate was reduced by greater than 4 logs almost instantaneously by the organic solvent/detergent step. In four other experiments, the concentration of both enveloped and non-enveloped viruses were decreased approximately 4 logs during the immunoaffinity chromatography step.

Further spiking studies have indicated inactivation of at least 11 logs of HIV-1 and at least 6 logs of HIV-2 by the solvent/detergent step of the Method M process.

HEMOFIL® M was administered to 33 patients previously untreated with Antihaemophilic Factor (Human). They have shown no signs of hepatitis or HIV infection following 3 to 15 months of evaluation (To be reviewed).

An ongoing study of 77 patients treated with HEMOFIL[R] M and monitored for 3 to 18 months has demonstrated no evidence of antibody response to mouse protein. (To be reviewed).

Reconstitution: Use Aseptic Technique

1. Bring Antihaemophilic Factor (Human), HEMOFIL[R] M, (dry concentrate) and Water for Injection, Ph.Eur., (diluent) to room temperature.

2. Remove caps from concentrate and diluent bottles to expose central portion of rubber stoppers.

3. Cleanse stoppers with germicidal solution.

4. Remove protective covering from one end of double-ended reconstitution needle and insert exposed needle through diluent stopper.

5. Remove protective covering from other end of double-ended needle. Invert diluent bottle over upright Antihaemophilic Factor (Human) bottle, then rapidly insert free end of the needle through the Antihaemophilic Factor (Human) bottle stopper at its centre. The vacuum in the Antihaemophilic Factor (Human) bottle will draw in the diluent.

6. Disconnect the two bottles by removing needle from diluent bottle stopper, then remove needle from Antihaemophilic Factor (Human) bottle. Swirl gently until all material is dissolved. Be sure that Antihaemophilic Factor (Human) is completely dissolved, otherwise active material will be removed by the filter.

Note: Do not refrigerate after reconstitution.

Do not use if a gel forms on reconstitution.

Administration: Use Aseptic Technique

Administration of Antihaemophilic Factor (Human), HEMOFIL[R] M should begin not more than 1 hour after reconstitution is complete.

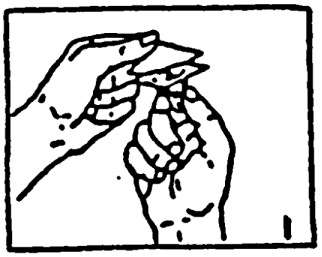
The reconstituted material should be at room temperature during administration.

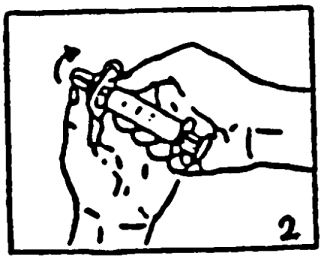
Intravenous syringe injection

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

1. After reconstituting the concentrate as described under "Reconstitution", open the filter spike package by peeling back the label of the blister pack (See Figure 1).

2. Hold the clear plastic blister pack at the rim of the filter spike and aseptically attach the filter spike to an empty plastic syringe. Twist the filter spike onto the syringe to ensure a secure connection. (See Figure 2)

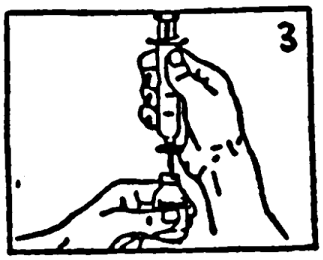


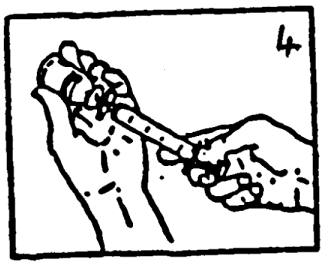


3. Draw back the plunger to admit air into the syringe.

4. Place the reconstituted Antihaemophilic Factor (Human), HEMOFIL® M bottle on a flat surface and while holding the bottle firmly to prevent slipping, insert the spike perpendicularly through the centre of the bottle stopper. (See Figure 3)

5. Inject air into bottle and then withdraw the reconstituted material into the syringe. (See Figure 4).





6. Remove and discard the filter spike from the syringe; attach a suitable needle or small vein infusion set and inject intravenously.

7. If a patient is to receive more than one bottle of Antihaemophilic Factor (Human), the contents of two bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. This practice lessens the loss of Antihaemophilic Factor (Human). Please note, filter needles are intended to filter the contents of a single bottle of Antihaemophilic Factor (Human) only.

Rate of Administration

Preparations of Antihaemophilic Factor (Human), HEMOFIL^{R} M, can be administered at a rate of up to 10 ml per minute with no significant reactions.

The pulse rate should be determined before and during administration of Antihaemophilic Factor (Human). Should a significant increase occur, reducing the rate of administration or temporarily halting the injection usually allows the symptoms to disappear promptly.

Information for Patients

Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis, and should be advised to discontinue use of the product and contact their physician if these symptoms occur.

HOW SUPPLIED

Antihaemophilic Factor (Human), HEMOFIL^{R} M, is available as a single dose bottle. Each bottle is labelled with the potency in International Units, and provided with 10 ml of Water for Injection, Ph.Eur. a double-ended reconstitution device,a filter spike, a 10 ml syringe and a 23 Ga miniset. miniset.

REFERENCES

1. Horowitz B., Wiebe M.E., Lippin A., et al: Inactivation of viruses in labile blood derivatives: 1. Disruption of lipid envèloped viruses by tri(n-butyl)phosphate detergent combinations. Transfusion 25: 516-522, 1985.

2. Prince A.M., Horowitz B., Brotman B.: Sterilisation of hepatitis and HTLV-III viruses by exposure to tri(n-butyl)phosphate and sodium cholate. Lancet I: 706-710, 1986.

3. Brinkhous K.M., Shanbrom E., Roberts H.R., et al: A new high potency glycine-precipitated antihaemophilic factor (AHF) concentrate: Treatment of classical haemophilia and haemophilia with inhibitors. JAMA 205: 613-617, 1968.

4. Shanbrom E., Thelin G.M.: Experimental prophylaxis of severe haemophilia with a Factor VIII concentrate. JAMA 208: 1853-1856, 1969.

5. Abildgaard C.F., Simone J.V., Corrigan J.J., et al: Treatment of haemophilia with glycine-precipitated Factor VIII. New Eng. J. Med. 275: 471-475, 1966.

6. Kasper C.K.: Haematologic care, in Comprehensive Management of Haemophilia. Boone D.C., (ed), Philadelphia, F.A. Davis Co., 1976, pp 3-17.

7. Hilgartner M.W.: Factor replacement therapy, in Haemophilia in the Child and Adult. Hilgartner M.W. (ed), New York, Masson Publishing U.S.A., Inc. 1982, pp 63-84.

8. Schimpf K., Rothmann P., Zimmermann K.: Factor VIII dosis in prophylaxis of haemophilia A; A further controlled study, in Proc XIth Cong. W.F.H. Kyoto, Japan, Academic Press, 1976, pp 363-366.

R Registered Trademark

Manufactured by: Hyland Division of Baxter Healthcare Corporation,
Glendale, CA 91202 and Lessines, Belgium.

Distributed by: Baxter Healthcare Ltd., Caxton Way,
Thetford, Norfolk.

PL.0116/XXXX
PA.167/X/X